2 family members who had a bleeding phenotype. Both family members who exhibited excessive bleeding events were found to have reduced thrombin generation, with a trigger of 5 pM tissue factor (TF) and very low levels of thrombin generation with 1 pM TF. Only partial correction of thrombin generation was observed in normal plasma mixing studies, suggesting the presence of a coagulation inhibitor. When thrombin generation was performed with a fivefold physiological excess of protein C with 5 pM TF as a trigger, thrombin generation for all family members was reduced compared with no change in control plasma. An anti-protein C antibody added to the plasma increased the thrombin generation to normal levels in the plasma from the affected subject, whereas in normal control plasma, the antibody did not make any difference. Plasma levels of thrombomodulin in the affected family members were elevated by 100-fold compared with normal plasma. When truncated thrombomodulin was added to normal plasma with thrombin generation determined by a 1 pM TF trigger of coagulation, a dose-dependent inhibition of thrombin generation was observed. These data confirmed the mode of action by which the affected family members were predisposed to an increased risk of bleeding.

This study therefore highlights that there is a “new kid on the block” to look out for when unexplained bleeding events in patients take place. With bleeding events, a systematic diagnosis through conventional tests to identify the cause of the bleeding in the first instance is performed. However, when these conventional tests appear normal, assessment of thrombin generation (using 1 pM TF) and measurement of plasma thrombomodulin levels may aid in the appropriate diagnosis prior to confirmation by genotyping in instances of bleeding where no other explanation can be found. The identification of this novel mutation in thrombomodulin may help to alleviate misdiagnosed bleeding events and enable suitable therapeutic intervention. This study also highlights the benefits of collaborative efforts of both clinical and basic science laboratories to address clinical problems.

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Comment on van Es et al, page 1968

Oral anticoagulants: new and improved

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In this issue of Blood, van Es and colleagues provide strong evidence that the new oral anticoagulants are safer and improve patient outcome.1 Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and/or pulmonary embolism (PE), is a very common condition, with an estimated 900,000 incident or recurrent events each year in the United States,2 and more than 1 million each year in the European Union.3 The standard treatment for most patients with VTE has been anticoagulant therapy with heparin or low-molecular-weight heparin for the initial 5 to 10 days, followed by an oral vitamin K antagonist, such as warfarin, for 3 months or longer.4 Vitamin K antagonists require laboratory monitoring of the anticoagulant effect and adjustment of the patient’s dose to maintain the international normalized ratio (INR) within the therapeutic range of 2.0 to 3.0.4 The need for anticoagulant monitoring complicates treatment, is a burden for patients, and is a major cost of therapy. To simplify treatment, new oral anticoagulant drugs have been developed that are direct inhibitors of either thrombin (dabigatran) or activated factor X (rivaroxaban, apixaban, and edoxaban), which have quick onset of effect and can be given in fixed doses once or twice daily without laboratory monitoring of the anticoagulant effect. During the last 5 years, 6 phase 3 clinical trials evaluating these drugs for the treatment of acute VTE have been completed and published.5-10 These trials included a combined total of >27,000 patients.5-10 van Es and colleagues provide a clinically useful synthesis of this data in a methodologically rigorous and carefully performed meta-analysis comparing the direct oral anticoagulants (DOACs) with vitamin K antagonist therapy.1 Because each of the phase 3 trials met the prespecified criteria for noninferiority of the efficacy of the DOAC for preventing recurrent VTE,5-10 the value of the work by van Es and coworkers lies in the added information it provides regarding specific major bleeding outcomes (intracranial bleeding and fatal bleeding), and regarding the risk–benefit profile in key patient subgroups commonly encountered by the clinician. These subgroups are patients presenting with symptomatic PE or symptomatic DVT, the elderly (age ≥75 years), the obese, patients with moderate renal impairment (creatinine clearance 30-49 mL/min), and patients with cancer. The authors appropriately evaluated possible heterogeneity in the results and have included a sensitivity analysis confined to the class of DOACs that inhibit factor Xa.

The results are positive for patients and clinicians. The DOACs were associated with clinically important relative risk (RR) reductions of 39% for major bleeding (RR 0.61), 63% for intracranial bleeding (RR 0.37), and 64% for fatal bleeding (RR 0.36).1 For each of these outcomes, the results are consistent among the trials; none of the trials has a point estimate for these outcomes in favor of the vitamin K antagonists (supplemental data). The number of patients who would...
The DOACs with currently recommended numbers of selected cancer patients were not included in the clinical trials, and cancer patients the benefit of should not be a reason to withhold from most. 

Regarding the key patient subgroups evaluated, the noninferior efficacy of the DOACs was consistent across all subgroups, with possibly superior efficacy in the elderly and in cancer patients. The safety advantage of reduced major bleeding was also consistent across the subgroups, except possibly in cancer patients, in whom the pooled estimate of a 23% RR reduction did not achieve statistical significance (supplemental data).

What are the implications for clinical practice? The DOACs should now replace vitamin K antagonists in most patients with VTE. The exceptions are patients with severe renal impairment (creatinine clearance <30 mL/min) because they were not included in the clinical trials, and cancer patients because only relatively small numbers of selected cancer patients were included and because clinical trials comparing the DOACs with currently recommended standard therapy with low-molecular-weight heparin have not been done. The lack of a specific reversal agent for the DOACs should not be a reason to withhold from most patients the benefit of significantly reduced risks of major bleeding, intracranial bleeding, and fatal bleeding. In the near term, vitamin K antagonists may be preferred in patients in whom prompt and measurable reversal of the anticoagulant effect will be required as a result of planned surgery or invasive procedures. The availability of an effective reversal agent for the DOACs is eagerly awaited and will further enhance their clinical utility. Because the DOACs do not require laboratory monitoring, patients receiving DOACs may have less frequent contact with their physician or anticoagulation clinic, and nonadherence to the prescribed therapy may not be detected as quickly. Physicians and health systems should use evidence-based strategies to enhance adherence, and they should evaluate patients at intervals to assess whether ongoing anticoagulant therapy is appropriate and maintained.

Some practical questions remain. Rivaroxaban and apixaban can be used as a single drug approach, whereas dabigatran and edoxaban are preceded by at least 5 days of heparin or low-molecular-weight heparin treatment. Is DOAC monotherapy sufficient for the full spectrum of VTE severity, or is “lead-in” heparin treatment preferred in some patients, such as those with PE who have right ventricular dysfunction? How does the effectiveness and safety of the DOACs compare with low-molecular-weight heparin treatment in cancer patients with VTE? If the DOACs are at least as effective and safe, they may improve the quality of life for such patients by avoiding daily subcutaneous injections. Clinical trials are urgently needed to address these questions.

Despite these questions, the results gained by van Es and colleagues provide further evidence that the DOACs are a major therapeutic advancement that simplifies anticoagulant therapy and improves patient safety outcomes in patients with VTE.

Conflict-of-interest: G.E.R. receives 

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Comment on Capitini et al, page 1976

Bringing out the DCs’ softer side in GVHD

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In this issue of Blood, Capitini et al use mouse models to demonstrate that STAT1 loss or inhibition causes dendritic cell (DC) modulation, resulting in lesser GVHD.

Graft-versus-host disease (GVHD) remains a significant cause of morbidity following allogeneic hematopoietic stem cell transplantation (HSCT). Much of the earlier research and approaches focused on the alloreactive donor T cell itself as the principal driver and mediator of GVHD. Approaches have ranged from simple removal of all T cells (which unfortunately also abrogates graft-versus-tumor [GVT] responses), blockade of costimulation or cytokine pathways, interfering with lymphocyte trafficking to GVHD target tissues, use of purified T-cell subsets (ie, memory cells,
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